Mike is a social professor of medicine and internal medicine and medical oncology. He shares patients or cancer patients, fraternity or cancers. As part of the smiling prostate, joining Allen 2009 Doctor Hertz was instructor of medicine at Harvard and attending physician in medicine at the Massachusetts General Hospital. MIKES graduate of Harvard College. He received his doctorate degree in cell biology from Rockville University’s and medical degree from Cornell University.
He completed a fellowship in Archology.

Dana Farber and postdoctoral fellowship in Biology, the Masters in Massachusetts, Channel MIT Institution might still be talking about the silk yellow cell therapy program for solid tumors.

Mike take it away.

Thanks, Dan.

Yeah, thanks everyone for inviting us from that from the therapy dog to talk.

I’m going to talk obviously about the solid tumor side and then the other half is going to be here as this would be talking about liquid.
So were the newest art. And we really started right before covid so we don’t have a whole lot of trials open, so I think that this talk is going to be sort of short on data, but I hope it’s going to be long on potential. OK, let me see if I can move my thing forward here in my disclosures. So the main therapies I’m going to talk about today are car T cells and tumor infiltrating lymphocytes. And I think that everybody is somewhat familiar with these terms. I know that a lot of people know
a lot about these so far, but they’re really quite different therapies, and I do want to talk a little bit about the basic biology. So for those who are immunologists, bear with us. Maybe read the newspaper for a minute or two while I give you my very simple oncologist’s View of immunology. So adaptive immunity is where T cells primarily recognize things that are foreign and used in attack them. Now,
one of the reasons we don’t attack ourselves is that we’re always taking little chunks of our proteins, expressing them on the surface in something called the major histocompatibility complex, and the T cell receptors. Basically, when were you know your own a little bit? After that all the T cell receptors that we have the T cells. That that recognized groups. That recognize. The energy is well, get deleted,
or at least they get turned off OK,
so generally we don’t respond
But if you get a foreign antigen like a bacteria,
what happens is let’s say if they go into a cell,
the cell chops up the proteins.
The proteins get put on MHC and the T cell receptor is going to recognize there’s going to be a strong interaction,
but that isn’t enough to actually cause killing.
It’s only when you get something
called costimulation OK, and that’s via another pathway. Another set of receptors. And then you actually get killed all right. So how can we use that information to kill cancer cells? So let me say a little bit more and go a little bit more in depth into the T cell receptor signaling first. So this is a schematic of the T cell receptor, the Alpha beta chains are the ones that actually recognize the antigens and MHC, and there are signaling molecules, the Zeta chain and the associated CD3. So T cell receptors only recognize proteins.
They only work if the antigen is expressed is presented by MHC. And they require Co stimulation. As I said, the signaling are through these two things. Antibodies another way that we recognize things that are formed were quite differently. They can recognize any type of management doesn’t have protein. They don’t use MHC. and antibodies are much, much stronger, their interactions with their antigens and T cell receptors are with their antigen that makes the interactions up.
So someone had the bright idea of taking the back end of a T cell receptor and connecting it to the front end of an antibody. And we call those guys chimeric antigen receptors and so this is the first generation car and this is actually in the 1990s. It was awhile ago so this is the antibody. OK on the outside of the cell and this is part of the solar spectrum. The inside of the cell worked a little bit, but not terribly well. A huge breakthrough though came in the second generation.
And here what was done is they add a domain to the protein of CD 28. And what’s that? Whoops, that of course is the costimulatory signal, and so when you put the customer let costimulator right in it, these are much, much more powerful, these are really what we mostly use today. There are even stronger ones. The third generations that use two costimulatory signals, and there’s the 4th generation, plus other genes that are put in
00:04:48.765 --> 00:04:50.787 to make the cells work better.
NOTE Confidence: 0.8157049
00:04:50.790 --> 00:04:53.300 So.
NOTE Confidence: 0.8157049
00:04:53.300 --> 00:04:55.256 When you actually the mechanics of
NOTE Confidence: 0.8157049
00:04:55.256 --> 00:04:57.569 this and in patients are complicated,
NOTE Confidence: 0.8157049
00:04:57.570 --> 00:04:59.706 just like all cell therapies are,
NOTE Confidence: 0.8157049
00:04:59.710 --> 00:05:01.130 whether it’s transplant or
NOTE Confidence: 0.8157049
00:05:01.130 --> 00:05:02.195 something like this.
NOTE Confidence: 0.8157049
00:05:02.200 --> 00:05:05.760 In this case you need to isolate the T cells.
NOTE Confidence: 0.8157049
00:05:05.760 --> 00:05:08.070 They have to get activated and then
NOTE Confidence: 0.8157049
00:05:08.070 --> 00:05:09.893 their transduced with the chimeric
NOTE Confidence: 0.8157049
00:05:09.893 --> 00:05:11.808 antigen receptor and then expanded
NOTE Confidence: 0.8157049
00:05:11.808 --> 00:05:14.041 and then reinforced in the meantime
NOTE Confidence: 0.8157049
00:05:14.041 --> 00:05:15.751 patients get lympho depleted and
NOTE Confidence: 0.8157049
00:05:15.751 --> 00:05:19.268 the reason for that is that.
NOTE Confidence: 0.8157049
00:05:19.270 --> 00:05:20.155 Probably twofold reasons.
NOTE Confidence: 0.8157049
00:05:20.155 --> 00:05:21.040 For some reasons,
you’re actually treating the cancer to some degree by lympho depleting, but that isn’t the case for all cancers. For some, you’re doing it to have a niche for the T cells to actually live in and grow it. As you might imagine, this does not take a day. This takes several weeks, so one of the things about this kind of treatment is patients have to be well enough to survive those weeks and to be able to tolerate the therapy. I’m not going to go into this in detail, but there are a lot of toxicities.
associated with these treatments.

NOTE Confidence: 0.77227306

The three famous ones are cited

NOTE Confidence: 0.77227306

kind of release syndrome,

NOTE Confidence: 0.77227306

which has to do with a lot

NOTE Confidence: 0.77227306

of T cells at the same time,

NOTE Confidence: 0.77227306

seeing antigen and then causing lots of

NOTE Confidence: 0.77227306

cytokines to go into the circulation.

NOTE Confidence: 0.77227306

There’s also neurotoxicity called

NOTE Confidence: 0.77227306

crests or cans and probably

NOTE Confidence: 0.77227306

the most severe of these HLH.

NOTE Confidence: 0.77227306

Alright, So what are we doing at Yale?

NOTE Confidence: 0.77227306

We have one party study open

NOTE Confidence: 0.77227306

right now for solid tumors.

NOTE Confidence: 0.77227306

This is a kidney cancer trial done

NOTE Confidence: 0.77227306

by the company, CRISPR Therapeutics.

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It’s anti CD 70 which is highly
expressed on clear cell kidney cancers

and then there’s some expression

on a few lymphoid type of cells.

Now it’s very long name for the trial.

The reason is that it’s actually

a little more complicated than

even what I described before.

‘cause these are allogeneic engineered

T cells. And what does that mean?

So these are T cells that actually don’t

come from the patient they come from.

Sort of healthy weight healthy donors

in whom there they’re having the car

but into their own T cells and they

this company using CRISPR CAS nine.
I think a lot of us are familiar with that to knock out certain other genes in these T cells to make them work in us. So what do I mean by that? Well, if you take someone else T cells and put them into you, they will attack you and you will attack it. It won’t be an effective therapy. They will get destroyed pretty quickly by the endogenous immune system, and they’re going to have off target effects tube via their T cell receptors, potentially. So what they’ve done this CRISPR therapeutics is in addition to
NOTE Confidence: 0.77227306
00:07:28.748 --> 00:07:30.884 putting in the car to these T cells.
NOTE Confidence: 0.77227306
00:07:30.890 --> 00:07:32.780 They’ve also put in using CRISPR.
NOTE Confidence: 0.77227306
00:07:32.780 --> 00:07:35.636 They’ve removed the T cell receptor OK.
NOTE Confidence: 0.77227306
00:07:35.640 --> 00:07:36.880 They’ve also removed something
NOTE Confidence: 0.77227306
00:07:36.880 --> 00:07:38.120 called beta two microglobulin,
NOTE Confidence: 0.77227306
00:07:38.120 --> 00:07:40.290 which is part of MHC class one,
NOTE Confidence: 0.77227306
00:07:40.290 --> 00:07:42.578 and the result is is that our immune
NOTE Confidence: 0.77227306
00:07:42.578 --> 00:07:44.197 system doesn’t recognize that it
NOTE Confidence: 0.77227306
00:07:44.197 --> 00:07:46.177 very well except by some something.
NOTE Confidence: 0.77227306
00:07:46.180 --> 00:07:47.420 All natural killer cells.
NOTE Confidence: 0.77227306
00:07:47.420 --> 00:07:48.970 It doesn’t do that much,
NOTE Confidence: 0.77227306
00:07:48.970 --> 00:07:50.640 and it doesn’t really recognize
NOTE Confidence: 0.77227306
00:07:50.640 --> 00:07:52.690 us except via the anti CD 7.
NOTE Confidence: 0.77227306
00:07:52.690 --> 00:07:53.001 Alright,
NOTE Confidence: 0.77227306
00:07:53.001 --> 00:07:55.489 so there are a bunch of advantages here
NOTE Confidence: 0.77227306

16
of using T cells from someone else and not from the patient one is speed. These cells are waiting. The patients don’t have to wait. Secondly, these cells are for someone with an immune intact immune system and a lot of patients with extensive cancers may not have intact immune systems and the T cells may be somewhat dysfunctional, cells may be somewhat dysfunctional, and obviously it leads to the potential for more of a drug, something that can be done with high levels of production out there for everybody we’ve enrolled.
One patient, we’re going to be enrolling one patient another patient in a few months, or at the dose escalation phase, and we’ll see how this trial goes.

Some of the challenges are for car T cells. Specifically in solid tumors. Well, in general there can be an issue with persistence. The car T cells. They may not last, but these are big issues for solitaire.
So one there is almost no answers in a solid tumor cannot lose. And when you give something like CAR T therapy against a particular antigen, it’s very likely that the tumor will just mutate or or lower expression of that antigen. And become resistant to it. In addition to that, the micro environment of the tumor is very toxic to a lot of immune cells, including T cells. It’s hard to infiltrate into a lot of tumors. There’s a lot of necrosis. Many of the cells have low blood supply, etc.
And finally, the toxicity is that I sort of mentioned before.

So one of the things that’s being done here is being done by the lab of City Chen. His is the only 11 going to talk about, but it’s worth pointing out there are many labs here working on car T type therapies. City Shuns Lab has developed a modular, high throughput way of developing cartis, and it’s the system that again is very complex. There’s a there’s no time for me to describe it and be I
wouldn’t be able to do very well anyway. But this is a slide from CD, this is his own system that he is designed using adeno associated virus. To make parties, it enables rapid building of new modules because because modular we can put in many different cars into a lot of cells and look at them in parallel. And it also allows for knockout of other genes in the cell just to make to try to improve the cell’s capabilities.
on a lot of the platforms that are used now in the short term goal, of course, is to generate better parties against kidney cancer. He’s actually looking at kidney cancer, which is great. ’cause that’s a lot of what I’m interested in, and we’re also working with Doctor Krueger on this area. Cougar, but also he can engineer in safety control so that if the T cells are causing some of these severe toxicities, they can be turned off. And you know the long term goal, of course, is to optimize better.
parties across solid tumors.

Anan maybe liquid tumors too.

In the first step of that,

but he makes a great car.

Is for us to actually put

moving on to till let’s go back

very quickly again into immunity.

So remember something for and it’s

a strong interaction by the T cell

receptor and the MHC complex you get

Co stimulation and you get killing.

Alright,

but how do you get a T cell that actually

kills something that’s not for it,
As mentioned before, we don’t interact very well with our own antigens. Now, cancer has sort of solved that a little bit for us in that cancer proteins are often mutated because cancer causing mutations and therefore the peptides actually can look for and so you can actually get T cells to kill. As we all know though, it doesn’t really work very well on its own. We need to give things like immune...
checkpoint inhibitors because of the toxic micro environment,
so I thought that was developed back in the 1980s. Was well,
maybe if we take the two T cells out of that environment, grow them up,
maybe we can cause cell killing if we re infuse those T cells.
And that’s what ’til therapy is.
So much like I described,
the car T cells,
you respect the tumors from patients.
T cells are isolated from those tumors.
They are activated an expanded in vitro,
NOTE Confidence: 0.8152212
00:12:20.520 --> 00:12:21.948 generally using Interleukin 2,
NOTE Confidence: 0.8152212
00:12:21.948 --> 00:12:24.090 but there are other interventions we
NOTE Confidence: 0.8152212
00:12:24.151 --> 00:12:26.495 use and then they reinfuse with the patient.
NOTE Confidence: 0.8152212
00:12:26.500 --> 00:12:27.493 In the meantime,
NOTE Confidence: 0.8152212
00:12:27.493 --> 00:12:29.148 agents have been limited depleted,
NOTE Confidence: 0.8152212
00:12:29.150 --> 00:12:31.496 which is extremely important for this
NOTE Confidence: 0.8152212
00:12:31.496 --> 00:12:33.953 therapy because we not only have to
NOTE Confidence: 0.8152212
00:12:33.953 --> 00:12:36.460 have a niche for the cells to go into,
NOTE Confidence: 0.8152212
00:12:36.460 --> 00:12:39.826 we have to get rid of T regulatory cells.
NOTE Confidence: 0.8152212
00:12:39.830 --> 00:12:41.050 And the Immune system Act
NOTE Confidence: 0.8152212
00:12:41.050 --> 00:12:42.270 as a sighted kind sink,
NOTE Confidence: 0.8152212
00:12:42.270 --> 00:12:44.111 sucking up all the good side accounts
NOTE Confidence: 0.8152212
00:12:44.111 --> 00:12:46.170 that we want to go to these T cells.
NOTE Confidence: 0.8152212
00:12:46.170 --> 00:12:48.662 'cause when we infuse these T cells
NOTE Confidence: 0.8152212
00:12:48.662 --> 00:12:50.828 we give patients in alluding to.
NOTE Confidence: 0.8152212
Now before I move on with that with till I think a lot of the time when I tell people that we're interested in cell therapies, they say oh it's cortisol therapy. But there's a huge difference is really between CAR T cell therapies and tils. As some examples. CAR T cells are MHC totally independent right there using an antibody, whereas 'til therapy is totally dependent. You know, car T cells are MHC totally independent right there using an antibody, whereas 'til therapy is totally dependent. CAR T cells don't? They can look at sugars or other non protein antigens. Tills do not.
Cars are pretty ineffective at looking at intracellular proteins. They’re working on that, so maybe we’ll get there one day, but right now they can’t really recognize a lot of the proteins. And the key thing is that you know, till can look at any antigens that they see. So for example, when we take tumors out of patience and isolate the lymphocytes from those, that’s going to be a diverse, diverse type of T cells, probably recognizing multiple different antigens.
And, as I said before, a big disadvantage of car T cells is that you can lose the one antigen they recognized in their useless and that may not be as big of an issue with 'til therapies. And Lastly, there toxicities are quite different. Alright, So what are we doing at Yale? We have a trial right now for looking at triple negative breast cancer. This is an IIT that I’m doing with IMS Therapeutics. This is the first dedicated breast cancer till trial world we’ve been. We’ve enrolled two patients so far,
and one of the reasons were interesting.

Breast is that there’s lab here.

Tristan Park, who’s a surgical oncologist here, an expert on breast cancer and on breast cancer cell therapies?

Who’s actually? Looking at the samples we get analyzing for the immune infiltrates and working with us on the trial.

Just to say a little bit more about what it actually entails. It’s there’s a lot of for any sort of cell therapy.

There’s a lot of work that goes into
it because these are complicated

therapies that require a good timing so

you know once a patient signs consent,

they have to get their surgeries.

Only then do you initiate.

Of course the till culture,

then it’s going to be going

for several weeks,

and once you know the till

is growing appropriately,

only then are you going to

limited Lee the patient and then

infuse that into the patient.

And then of course,

as I said,

these people require oil to afterwards,
and they’re going to be in the hospital for a lot of this because they’re going to depleted and then once they recover, we follow them.

So, how might we improve some of these things? I think infusion and reception isolation. That’s not where the money is, but clearly we can maybe improve activating and expanding these cells and make them better killers. And the people who are the best at growing up and activating these cells.
Of course that you are the people of the Advanced Therapy Lab run by Alexi Burst. Never die across and they have a huge amount of expertise over many years. Looking at till type therapies. They’ve grown up a lot of different cell products for use in patients, and I actually hold Inds for growing Melanoma till, but of course they actually did it and we’re working together right now to grow up lung cancer till four, ideally to eventually put into patients. Just quickly to point out, they are very good at growing up selves.
This is 1 experiment which they actually separated out the PD one positive from negative cells and show a lot of expansion in both of them and this just kind of shows one experiment of theirs that the cells they get are actually quite good. So here till they’ve isolated out and these are assays for interferon gamma production which is an essay of sort of it’s a surrogate for cell killing and when you take this pill and you put him. Alone, they don’t make a lot of interferon gamma.
As soon as you put them with autologous tumor, or they recognize antigens in the setting of MHC, they make tons of interferon gamma and then if you give them someone else's tumor that has emerged, they don't recognize they don't kill. So they're very good at making cells that kill and kill specifically, which is exactly what we need. So what can we do to actually improve things? To make these, what are we interested in doing here? Yale to improve these therapies?
00:17:17.387 --> 00:17:19.709 doing experiments to look at adjusting
00:17:19.709 --> 00:17:22.594 the growth medium that that they do
00:17:22.594 --> 00:17:24.739 it in different cytokine combinations,
00:17:24.740 --> 00:17:26.590 different levels of cytokines and
00:17:26.590 --> 00:17:28.070 those experiments are ongoing.
00:17:28.070 --> 00:17:29.895 But. It’s actually striking how
00:17:29.895 --> 00:17:32.093 little we know about what happens
00:17:32.093 --> 00:17:34.200 between when we take the cells out
00:17:34.200 --> 00:17:36.537 of a person and we expand them.
00:17:36.540 --> 00:17:37.808 We don’t really know
00:17:37.808 --> 00:17:39.076 which cells get expanded.
00:17:39.080 --> 00:17:41.792 We don’t know whether the T cell maturation
00:17:41.792 --> 00:17:44.170 states whether they are more naive or more.
00:17:44.170 --> 00:17:45.442 Effector cells dictate which
00:17:45.442 --> 00:17:46.396 cells that expanded.
We don’t know how this concept of T cell exhaustion relates to expansion, and we have very little idea about how homogeneous or heterogeneous that essential traits are between tumors or between tumor types. So can we actually do experiments to figure some of this stuff out? And the approach that we’re going to take here, and we’ve actually begun taking, is to do single cell RNA sequencing and paired with TCR sequencing so that we can follow specific T cell clones through growth and figure...
out which maturation phenotypes are the ones that grow the best. And whether exhaustion has an effect, one it's being done beginning, and Sam Katz is lab by Sam Kerr, one of his graduate students, and I'll be doing some of these studies on long till.
so I don’t know where I am on time and
someone told me I’ve got a little time.
OK,
So let me say one last set of
experiments that are being done at Yale.
Looking at some basic science that could
have a big impact on T cell therapies.
And by the way, I should point out that,
you know, I’ve mentioned a
few people who are doing work,
but there are many others doing work at Yale.
I they don’t have time unfortunately,
but but I don’t mean to
leave other people out.
We’re doing really vital stuff that
In fact, probably there are a lot of things I don’t know about that. I wish I did.

So one of the things that Sam Katz’s lab is working on for quite awhile.

Weismann’s lab is working on is the idea of mRNA reprogramming?

So he’s using something called crisper I which is a crisper based technique to knock down genes but not to actually cause mutations or changes the actual DNA.

The advantages of this technique is that you can do multiple RNAs at once.
00:19:46.250 --> 00:19:49.045 Sorry bout that. The.
NOTE Confidence: 0.83190864
00:19:49.045 --> 00:19:51.055 Other thing about this of course
NOTE Confidence: 0.83190864
00:19:51.055 --> 00:19:53.710 is when you do these things by RNA.
NOTE Confidence: 0.83190864
00:19:53.710 --> 00:19:54.544 RNA is temporary,
NOTE Confidence: 0.83190864
00:19:54.544 --> 00:19:56.212 so there are pluses to that
NOTE Confidence: 0.83190864
00:19:56.212 --> 00:19:57.460 and minuses to that.
NOTE Confidence: 0.83190864
00:19:57.460 --> 00:20:00.196 The pluses are that it’s a lot safer.
NOTE Confidence: 0.83190864
00:20:00.200 --> 00:20:01.528 Not permanently altering itself.
NOTE Confidence: 0.83190864
00:20:01.528 --> 00:20:02.856 OK, the negative, however,
NOTE Confidence: 0.83190864
00:20:02.856 --> 00:20:04.516 is that it’s only temporary,
NOTE Confidence: 0.83190864
00:20:04.520 --> 00:20:06.725 so if you want to have effects
NOTE Confidence: 0.83190864
00:20:06.725 --> 00:20:08.499 that last a long time,
NOTE Confidence: 0.83190864
00:20:08.500 --> 00:20:12.865 this might not be the method to do it.
NOTE Confidence: 0.83190864
00:20:12.870 --> 00:20:15.054 But you can imagine situations where using
NOTE Confidence: 0.83190864
00:20:15.054 --> 00:20:17.462 this kind of technique you could really
NOTE Confidence: 0.83190864
00:20:17.462 --> 00:20:20.089 turbocharge a cell for short period of time.
So for example, we could have a car T cell. And you could use his technique to make the groups make them particularly proliferative at the time at inside accounts, for example to happen particularly powerful and killing stimulators of other things, you could have inhibitors of negative regulators, and in fact Sam is shown in his lab and from Weismans lab that for example they can at the same time using their CRISPR RNA I techniques, Christmas learning techniques.
to increase IL two in a cell.
And decrease BCL type proteins
which are made up tatic proteins.
So again when you think about what
I've talked about so far with,
let's say the city Chen Lab in which
they can do multiple different things
to design sort of permanent T cells,
that car T cells that are
particularly powerful.
You could also imagine adding in
these M RNA’s to those same cells and
making turbochargers even more so.
There's a huge amount of
combinatorial things that we could do.
To improve his cell therapies,
and there’s a lot of excitement for all those things. Last but certainly not least, I just want to acknowledge all that people have been doing a lot of work. So what first assault therapy DART 3 docs? Who do it right now or are nearest Stewart and I Alex is our CDT N as fantastic Sharon days are relatively new but also fantastic research nurse Ann Pavan or CRA. I’m not impressed but and then we have an amazing team here doing, you know regulatory and and pharmacy etc. Also, of course, the AC T lab.
Which you know is really going to be the people developing. Sorry the next therapies that we do here, I mentioned the Melanoma team because, really, we’ve been doing till at Yale for very long time. And the person who got us started here was Mary Otional and a lot of the ideas that I talked about with regards to how to study these things really came from Mario. Harriet has done the most to have anybody here and has done a huge amount and Sarah Weiss has seen. A lot of the patients as well,
Katrina Bezak, is the person who is really a point person for a lot of salt therapies here, and she’s actually also key for setting us up for. As I said, the very very likely approval of heart till in Melanoma people probably don’t know this, but we have our own something called CDC which is for cell therapies. It’s a committee to look at really usage and whether we have the capability and the capacity. To do all the different trials we want to do,
none of this would be possible without the nursing staff on 11/12 North.

A pheresis machine, Hendrickson the RSL, Audrey King, and of course, the lab.

As I mentioned, and I should point out, that as I said, we're trying to get an Ind right now for long till. And that's based on funding we got from the office floor, and I think I'll leave it at that.

Thanks everybody.

My great presentation. Really excellent.

Let's see if there any questions from the audience chat room here.

So this is from God.
00:23:56.120 --> 00:23:57.940 Looks like you’re so excited.

00:23:57.940 --> 00:24:00.040 Talk research on adding tablets and

00:24:00.040 --> 00:24:02.532 margin molecules or modules in T cells

00:24:02.532 --> 00:24:04.252 to get around challenging metabolic

00:24:04.252 --> 00:24:05.950 environment for exhaustion times.

00:24:05.950 --> 00:24:09.219 So there are there have been, you know, a

00:24:09.220 --> 00:24:12.226 lot of they’re going to have a bunch of

00:24:12.226 --> 00:24:15.045 studies in mice that are really fantastic.

00:24:15.050 --> 00:24:17.228 Actually, some of the best ones.

00:24:17.230 --> 00:24:19.420 I think we’re from Sue Keck,

00:24:19.420 --> 00:24:22.692 used to have a cancer biology lab cancer

00:24:22.692 --> 00:24:25.286 Menology lab here and now she’s at.

00:24:25.290 --> 00:24:28.231 Assault or or scripts.

00:24:28.231 --> 00:24:29.339 I don’t know which,

00:24:29.340 --> 00:24:32.208 but she’s in California, but absolutely.
So there's no question that in mice you can knock down metabolic pathways, making T cells much more tolerant of the toxic micro environment in the tumor. Now that hasn't yet been done in people. People have been doing screens to look at to make T cells more effective, and either party or till, and so there might be a company out there that has done that, or we just don't know. Absolutely, that's a huge area of research.
by a lot of people, and I think we will definitely at some point the future be seen. Carty cells that have metabolic pathways altered based on this. This is some recent data looking Dyson kinase and using that as a way of overcoming, I'll. There being no troubles me design right now. Look at this picture. Next comment is from Marcus Poison Bird. Nice presentation, just to mention. Let’s try this myself. Every efforts include developing
00:25:44.828 --> 00:25:45.570 Massapequa tillmanns.
NOTE Confidence: 0.63548505
00:25:45.570 --> 00:25:46.310 Yes, absolutely.
NOTE Confidence: 0.63548505
00:25:46.310 --> 00:25:48.540 I need to talk to you.
NOTE Confidence: 0.63548505
00:25:48.540 --> 00:25:49.650 And Marcus, yes,
NOTE Confidence: 0.6581466
00:25:49.650 --> 00:25:51.130 very excited about that.
NOTE Confidence: 0.7907089
00:25:52.890 --> 00:25:53.454 Ask questions.
NOTE Confidence: 0.7907089
00:25:53.454 --> 00:25:54.864 Have party studies been performed
NOTE Confidence: 0.7907089
00:25:54.864 --> 00:25:56.132 patients in multiple Kartik
NOTE Confidence: 0.7907089
00:25:56.132 --> 00:25:57.254 loans simultaneously against
NOTE Confidence: 0.7907089
00:25:57.254 --> 00:25:58.376 multiple different energies?
NOTE Confidence: 0.7907089
00:25:58.380 --> 00:25:59.668 How many tourists again,
NOTE Confidence: 0.7907089
00:25:59.668 --> 00:26:00.956 is it generally available?
NOTE Confidence: 0.7907089
00:26:00.960 --> 00:26:02.252 Is detention targets in
NOTE Confidence: 0.7907089
00:26:02.252 --> 00:26:03.867 different types of solid tumors?
NOTE Confidence: 0.7907089
00:26:03.870 --> 00:26:05.158 So I don’t know
NOTE Confidence: 0.7907089
00:26:05.160 --> 00:26:06.520 the answer to that,
but I can tell you what I do now.

So I think the idea of using multiple parties at once.

I think there’s a worry that when you do that and I think their data for this that multiple ones within a cell result in a decrement of the actual response that you need to have.

A lot of the same.

You need to have sort of.

The same cars activate it all at once to really get a good response.

We have too many androgens.

It doesn’t, I think,

work as well like you basically.
dilute out the response.

That’s what I think.

He basically diluted out.

Now there are there have been people who

are designing right now parties that are.

Their heritage,

their heterodimers,

so one of the antibody

chains is to one target.

One of the antibody chains to another

target that’s only going to work if you

have really high levels of both antigens.

Obviously on the cell,

but those are inexperienced or those

are being experimented on right now

and we’ll see how those those work.
There's a real question about if you do that, you're not going to get the binding is not going to be as good regarding the number of tumor specific antigens. Again, it probably varies from cell to cell. That the older studies seem to indicate that these are very old studies, so it's very hard to know what that means. But for the till studies in some of the patients, when I looked at the ones who had really good responses. It did look as though. It was usually one dominant clone. Sometimes there were two dominant clones.
It’s hard to know exactly what those data were. A very limited number of patients, and it’s hard to know that they were looking at the right time. Like maybe the clone was there did a lot of what it’s supposed to do, and then a lot of it disappeared from the blood for some reason, so it’s very hard to know how much that’s real. The last thing I would say, though, is that it looks as though the most important antigens are private neoantigens, meaning they’re not these big targets that we do, and that’s really a worry.
for car T cells in general,
for solid tumors.
So that is sort of a separate issue.
Terrific Mike is always great presentation,
like to move on to our second speaker,
Doctor IRA, Sufi doctor Susan,
System Professor of Medicine and Hematology Co.
Directed the adult Carty salty program.
She received her medical emergency nurse in New York at Stony Brook
and completed a fellowship at Yale
University School of Medicine.
Doctor seems clever work is in the area of hematological in season.
Tallest algic stem cell transplantation
NOTE Confidence: 0.6741931
for his commissions as part of New Sweden
NOTE Confidence: 0.6741931
legacy programming transplant teams.
NOTE Confidence: 0.6741931
She developed a strong interest
NOTE Confidence: 0.6741931
promised she's focused her efforts
NOTE Confidence: 0.6741931
in treating patients with aggressive,
NOTE Confidence: 0.6741931
more focus as part of clinical
NOTE Confidence: 0.6741931
trials solid in the response to
NOTE Confidence: 0.6741931
treatment without August or outdated.
NOTE Confidence: 0.6741931
Translate based on the specifics
NOTE Confidence: 0.6741931
of specific seeds.
NOTE Confidence: 0.6741931
As to director of the car T cell therapy
NOTE Confidence: 0.6741931
product Spell Cancer hospital doctor Soupy.
NOTE Confidence: 0.6741931
As part of a team that brings
NOTE Confidence: 0.6741931
interview Milliman therapy treatments
00:29:17.623 --> 00:29:19.373 options to patients with certain types of blood cancers doctors.

00:29:22.460 --> 00:29:24.728 Thank you very much for having me.

00:29:36.100 --> 00:29:37.360 Can you see my slides?

00:29:39.860 --> 00:29:44.660 Now you know. Well, you know I have.

00:30:15.820 --> 00:30:16.290 Yeah.

00:30:22.050 --> 00:30:24.654 Thank you so my focus today is going to be in South therapist malignancies and what we’re doing here at Yale.

00:30:36.100 --> 00:30:37.360 I’m a clinical investigator in lymphoma and cell therapies.

00:30:41.590 --> 00:30:44.908 I have a couple of bad disclosures.
So the I’d like to update you today on some of the FDA approved indications for cell therapies and malignancies, which are growing by the day. Some of our research strategies to improve response rates and prevent resistance to cell therapies. Some of the challenges we’re facing clinically and research wise. And then I’d like to end the presentation by giving you an idea about the work that we’re doing here at DL as part of our immune cell therapy dart for hematologic malignancies and then some of the Inter institutional research collaborations that we
have started to work on.
So, as Mike mentioned,
there’s been an evolution in
chimeric antigen receptors.
Overtime,
the once we are still using in the
clinic that are commercially approve,
our second generation cars,
but there is some innovative card
design going on including suicide
cars as a control mechanism for
better toxicity management.
This dual targeting cars that express.
Two different antigen specific
cars by specifics where you have.
Add two linked SF Sfes within one core vector and then these TCR mimic cars that are important to address HLA presented antigen swear. You’re directing the CFP domain against a peptide HLA complex. Initially the the target was CD 19 for B cell malignancies because as you all know it’s a pan bissan marker, its expression is generally restricted to B cells and their precursors and represent it’s it’s surface molecules, so it’s represented irrational target for therapy and he malignancies and so all of the agents that are approved for commercial use.
Or directed at city 19. So we started initially back in 2019. The first approval with that DISA, gentle occlusal in pediatric LL and subsequent to that we’ve had a series of approvals including this agenda, Cluzel and Axicabtagene Silo Loosle for aggressive diffuse large B cell lymphoma, transformed follicular lymphoma and then. Lisso catagen merilou. So where you are giving the cells differently because it’s a defined CD4 to CD8 ratio, so there is some novelty compared to the two previously approved products and then more recently Brexit.
catagen auto loosle just in the last year for mantle cell lymphoma.

Anan, finally, you know just a few weeks ago Axicabtagene Silo Loosle for relapsed refractory follicular lymphoma. So the response rates that we see with these drugs, particularly in low grade lymphomas like follicular, are extremely good with very high overall response rate and complete response rates in pretreated patients, and then in diffuse large B cell lymphoma and aggressive deal BCL or transformed the complete response.
rates have varied anywhere from 30 to 50% even though the initial overall response rates. Are very high, so these are still very good outcomes. Don’t get me wrong for this group of patients, you know the predicted long term. Survival is typically less than 10% when they go on to get CAR T cell therapies. So we’ve really been able to to cure a good subset of those patients. But as you can see, you know we still have a long way to go in aggressive lymphomas be cause.
Even of the patients were cheap

Even of the patients were cheap

Complete remission only about 2/3 are able to maintain that, but it’s very.

It’s very exciting because just in the last couple of years we now have all of these products that are commercially approved for use and that we are already using here at Yale.

So the other rational target was BCM may in multiple myeloma, which is highly expressed on malignant plasma cells.

And we know that higher concentrations of soluble BCM mayor also associated with poor outcomes.
This is very essential in regulating B cell maturation and differentiation. And so there have been a series of phase one and two studies looking at PCM. A directed car T cells. And particularly the first one I did, captain be cluzel, is actually very close to approval. These were very heavily pretreated patients with a median number of treatments being about 6. And as you can see, the overall response rates are extremely good and even complete response rates.
There is of course toxicity like we saw with anti CD 19, particularly cytokinin release and neurologic toxicity, but again this is a very difficult population of patients to treat. The majority of them were what we call triple refractory to emits an proteasome inhibitors and about 25% of patients were pent. Artifactory, These are extremely good outcomes for this. For this patient population. And there’s now a race to get FDA approval in the USA.
Not just only for I decapped agenda cluzel but but also for. For several other products and there are efforts being made to introduce them earlier in earlier phases of disease and comparing them to the standard of care which is autologous stem cell transplant. And then there are already efforts being made to mitigate antigen escape by combining. For example, PC MA Carty with CD19 CAR targeting other other antigens. So the same cannot be said for acute myeloid leukemia, unfortunately, which has been, you know,
a great challenge over the years. And because many of the potential target antigens are actually intracellular, their tumor associated antigens or NEO antigens and the proteins that are expressed on the surface of the malignant leukemic cells, like City 33, you know some of those markers are also expressed on. Hammer away **** stem cells and so. The trials going on have had to consolidate. Cortisol therapy or or rescue I should say the the mirror with an allogeneic stem cell transplant. So there are several critical
and resolved issues with car T cell therapy in he malignancies, and I would categorize them in failure to achieve remission, disease, relapse, toxicities with car T cell and then some of the toxicity. Some of the challenges in moving beyond Bissell LL and diffuse large B cell lymphoma, two other diseases that may not necessarily. Have high expression of surface markers. Easy to visit that are easy to target with cortisol therapy or certain diseases where. Malignant clone, residing inside a lymph
node and not necessarily in the circulation. Like with Abyssal LL and so there’s that challenge of the tumor microenvironment prohibiting the T cells from getting there.

So. What is it that? Predicts outcome from a patient perspective. Ann and risk factors that we can outline before they go onto car T cell therapy. So there was this large study that looked at baseline factors that were associated with worse overall survival and progression free survival in patients who got standard of care. Axicabtagene, Sila Loosle and as you can see here, there were several factors that were
00:40:30.032 --> 00:40:31.433 statistically significantly associated.

00:40:31.440 --> 00:40:36.588 With worse outcomes and in particular.

00:40:36.590 --> 00:40:44.039 I would outline here patients that had high bulk of disease and patients that had,

00:40:44.040 --> 00:40:45.058 for example,

00:40:45.058 --> 00:40:47.603 elevated LDH levels pre transplant

00:40:47.603 --> 00:40:49.633 patients who required bridging therapy also were at higher risk

00:40:49.633 --> 00:40:52.159 of having worse overall survival and progression free survival,

00:40:52.159 --> 00:41:00.330 perhaps because both of these things are a surrogate for a higher disease burden,

00:41:00.330 --> 00:41:03.917 and then Interestingly some of the other factors that were associated with outcomes.

00:41:03.920 --> 00:41:10.438 Were younger age and also

00:41:10.440 --> 00:41:13.065 Was younger age and also
male gender and that is. Very different from what we see. Included in our prognostic indices for lymphomas where actually older patients tend to do worse, and this means that we need to really, really look at our prognostic markers in the era of cell therapy and redefine what relevant clinical risk factors are. So this is showing a multivariable model of Afexa cottage inside a looser treated patients, where again having.
high LDH levels is associated with worse progression, free survival and overall survival. And then what about, you know, the disease itself? One of the things that we already know is that about 25 to 30% of patients who relapse after car T cell therapy. Experienced loss of CD 19 and this was demonstrated. Inazuma 1 trial and the US Carty Lymphoma consortium. So it’s not the majority of patients, particularly in lymphoma, but it is a good subset and so you know what.
What can we do? To prevent antigen loss and then also this PD One PDL, one mediated cortisol inhibition and so. Because we know that PDL one up regulation is actually contributing to Carty exhaustion so. We have this publication nice publication in Nature Medicine from 2020, where. Nirav Shah at. In Wisconsin, actually looked at point of care manufactured by specific anti CD 20 and anti CD 19 CAR T cells in relapsed malignancies. In some of these patients had already undergone anti CD 19 CAR T cell therapy.
And they do see ongoing responses in about 40% of patients,
I think out of about 60% that responded initially and they did not observe loss of CD 19 in progressing patients when they.
Target at the tumor with the by specifics. So really very very exciting data.
And then just this year.
Just this past year at ASCO. They presented results of a first CD targeting Bicistronic which is dual antigen targeting.
With humanized binders, to reduce image unicity, and in addition to 41 BB costimulatory,
they also edit OX 40 to improve persistence.

So based on that? Data they went on to do a single arm open label multicenter phase. One two study where they did tool dual targeting of CD 19 and CD 22. But they also added Pember Lizum app for relapsed refractory diffuse large B cell lymphoma and Interestingly. What they saw is there is a high rate of complete response is about 66%, although it’s too early to say you know how. If they’re going to be durable and how durable they will be, because right now they. They only have short term a data,
but Interestingly there was very little toxicity with this particular construct. They did not see any grade three or four cytokine release or neurologic toxicity. And that perhaps really is a reflection of this. Really novel novel technology that they’re using with a novel pentameric spacer, using with a novel pentameric spacer, and this humanized binders so this data is very exciting because it’s a therapy that we might be able to a therapy that we might be able to use if approved eventually in the outpatient setting and delivered in the outpatient setting. And that’s where they’re really
going with this. So I'm. 
What else do we know about the?

The disease aspect itself that may
make response to cortisol therapy.
Challenging,

so this data from the Juliet study,
which was the global phase two trial
of tisagenlecleucel in relapsed
refractory diffuse large B cell lymphoma.
They looked at the Myc expression and
tumor infiltrating T cells in that study,
and what they actually found was
that baseline mic negative status
was actually associated with
significantly improved outcome
compared to Nick positive patients.
And that included also longer median duration of response and overall survival. And when they looked at the tumor microenvironment analysis of the baseline biopsies, what they saw is that lack or low frequency of tumor infiltrating CD3 positive T cells was also associated with short progression free survival compared to patients that had more than 3% CD3 T cells. In the tumor so taken together, these results suggest that make overexpression or an unfavorable immunosuppressive tumor microenvironment.
with a restricted T cell response

may impact score efficacy in patients with large B cell lymphoma.

And then this publication and Oncotarget looked at mutations or copy number losses of CD58 and TP53. Genes in diffuse large B cell lymphoma and showed that these are independent unfavorable prognostic markers so.

This is actually binds CD two and the T cells and T cell mediated cytotoxicity and also NK cell mediated cytotoxicity is actually quite important. And quite dependent on the expression of CD 58.
On the tumor tissue.

So in Ash 2020 they presented data looking at city 58 mutations and circulating tumor DNA is tumor DNA and they showed that this was associated with poor outcome. After Axicabtagene sila loosle. These 358 mutations are or loss are common and they occur in about 20% of patients with diffuse large B cell lymphoma and then in addition to that the protein City 58 protein expression is also directly related somewhere between 60 to 80% to 70% of patients with diffuse large B cell lymphoma.
His do regulate have deregulation of the CD 58 protein expression. And as you can see here, they were able to show that loss of this expression was also associated with worst outcomes were in blue. Here you see 5058 wild type and 58 alteration so. Fewer patients that had loss of CD 58 expression actually went on to achieve complete remission. The majority either did not respond or they achieved only partial remission. And then they went on to to progress, unfortunately. So, meisner. Amazing group.
Presented this data very, very interesting this year at ASH where they showed that integrating City 22 costimulation within cars was actually able to overcome City 58 loss in tumor cells and they tried this both insists an entrance and it wasn’t until they integrated it entrance that they saw these. These results so. This was very eye opening for us because, we used to think that. All of the Co stimulation is coming from other cells. And we didn’t really realize how
00:50:48.720 --> 00:50:52.501 important actually ceded to City to
NOTE Confidence: 0.36321577
00:50:52.501 --> 00:50:56.400 was in in car mediated cytotoxicity.
NOTE Confidence: 0.36321577
00:50:56.400 --> 00:50:58.689 So City 5862 was a very novel
NOTE Confidence: 0.36321577
00:50:58.689 --> 00:51:01.530 axis of car resistance that was
NOTE Confidence: 0.36321577
00:51:01.530 --> 00:51:03.894 uncovered through deep correlative
NOTE Confidence: 0.36321577
00:51:03.894 --> 00:51:06.665 studies in patients getting cell
NOTE Confidence: 0.36321577
00:51:06.665 --> 00:51:08.945 therapies and city 58 loss,
NOTE Confidence: 0.36321577
00:51:08.950 --> 00:51:11.740 or mutation pretends a poor outcome,
NOTE Confidence: 0.36321577
00:51:11.740 --> 00:51:14.974 but perhaps we can overcome that by
NOTE Confidence: 0.36321577
00:51:14.974 --> 00:51:17.303 engineering these cars that integrates
NOTE Confidence: 0.36321577
00:51:17.303 --> 00:51:20.313 it is 2 signaling in entrance and
NOTE Confidence: 0.36321577
00:51:20.313 --> 00:51:23.257 this is important because City 58
NOTE Confidence: 0.36321577
00:51:23.257 --> 00:51:26.115 Lawson mutations are also common in.
NOTE Confidence: 0.36321577
00:51:26.115 --> 00:51:28.665 Other cancers in are likely able
NOTE Confidence: 0.36321577
00:51:28.665 --> 00:51:31.101 to mediate resistance to other
NOTE Confidence: 0.36321577
00:51:31.101 --> 00:51:32.727 cars and immunotherapeutics,
so it could perhaps be applied in other malignancies outside of diffuse large B cell lymphoma.

So I've spoken to you about the relapse reflect setting, but we are now doing studies pushing these cellular therapies in the second line, and even in the first line settings, Uma 12 looked at very high risk patients with high grade B cell lymphoma. With Myc, BCL, two and BCL 6 translocations, and they did pet directed therapy and for patients who still had disease after two cycles by PET scan.
They actually went on to get their T cells collected and then receive Car T cell therapy. So these are the results. They saw a very high 85% of the overall response rate with 74% CRS. This is a difficult group of patients for us to treat because oftentimes they do not achieve remission and they progress right through therapy. The car T cell expansion was greater in this study when compared to Zuma one which were. Patients with relapsed refractory disease were treated so so higher quality T cells with higher,
00:53:00.660 --> 00:53:03.548 with higher higher proliferation
NOTE Confidence: 0.36321577
00:53:03.548 --> 00:53:05.714 and higher expansion.
NOTE Confidence: 0.36321577
00:53:05.720 --> 00:53:07.324 So this has not.
NOTE Confidence: 0.36321577
00:53:07.324 --> 00:53:10.229 Obviously it’s not prime time for us
NOTE Confidence: 0.36321577
00:53:10.229 --> 00:53:12.314 to change our decision-making and
NOTE Confidence: 0.36321577
00:53:12.314 --> 00:53:15.589 move this to to first line therapy,
NOTE Confidence: 0.36321577
00:53:15.590 --> 00:53:18.410 but there is definitely improved T
NOTE Confidence: 0.36321577
00:53:18.410 --> 00:53:21.149 cell fitness in first line treatment
NOTE Confidence: 0.36321577
00:53:21.149 --> 00:53:24.734 and this may be the wave of the future
NOTE Confidence: 0.36321577
00:53:24.734 --> 00:53:27.597 when we get more long term data.
NOTE Confidence: 0.36321577
00:53:27.600 --> 00:53:31.024 So just to sort of recap for you,
NOTE Confidence: 0.36321577
00:53:31.030 --> 00:53:34.414 some of the studies in relapsed
NOTE Confidence: 0.36321577
00:53:34.414 --> 00:53:36.106 refractory disease and.
NOTE Confidence: 0.36321577
00:53:36.110 --> 00:53:38.606 Also to include some data with
NOTE Confidence: 0.36321577
00:53:38.606 --> 00:53:41.110 CLL and mantle cell lymphoma,
as you can see very high overall response rates across the board and then somewhere between 50 and 75% complete remission rates in relapse patients. So where are we going with this? As I mentioned, we’re trying to introduce them earlier in the lines of therapies. So many phase three studies looking at second line for transplant eligible patients, randomizing them to transplant versus Carty and then perhaps eventually in the front line and then in a LL. Patients looking at patients one or MRD positive after one line of therapy.
And then hopefully some of these phase three data in adults will result in an approval because we still don’t have an approval in a LL for patients over the age of 25. So what about alginate cars is, as you know, there are some limitations with autologous CAR T cells, particularly in terms of cost harvesting and manufacturing failures and disease really progressing during manufacture, and we can really bypass a lot of that with donor derived. Sales where we can really reduce the time to infusion significantly and actually
be able to take more patients to Carty.

And there's an increased probability of healthy cortisol generation and the convenient of repeat dosing if necessary.

So these are some of the investigational allogeneic CAR T cells for him malignancies.

Targeting different antigens both in lymphomas AALL, but also in multiple myeloma.

This is still early phase one phase two data,

but I think that this is going to be the wave of the future in Carty,

so I'm going to now shift gears to just briefly talk about our cortisol therapy program here at heel we started our efforts in 2018 and were.
Able to eventually treat our first patients in January of 2019 and then were able to actually achieve fact accreditation after extensive auditing of our program. So this is our organizational chart. As you can see, it includes collaboration between multiple different departments. Physicians nursing program self therapy with Diane and Alexianne. We have a really trained group of people being able to freeze the patients and
then and then give the conditioning

therapy and manage the toxicities.

So what have we done in the last two years with 357 patients, some of them with axicabtagene, sidlu,

We're just starting to actually expand to mantle cell lymphoma

And we've also treated 11 patients on clinical trial for multiple myeloma

And as Mike mentioned there are some there is much less toxicity.

But there are also challenges in terms of.

In terms of the short life of the mRNA,
and perhaps the need for frequent dosing or maybe introducing this in earlier lines of therapy where patients do not have are not very heavily pretreated and do not have an extensive burden of disease with a new approval and multiple myeloma expected this year, there’s actually an anticipated significant rise in numbers of patients that were going to be treated. And what that means is that we can collect a lot more data and do a lot of studies on patient samples. So this is the yellow advanced cell
therapy lab and then this is our

that Mike and I call lead and and

I won’t belabor this,

but we wouldn’t be able to do what

we do without their amazing work.

So this is our portfolio.

We have some studies that were

opened and finished accrual,

but as you can see we have a large number of.

Pending studies at the majority of

which are very novel because they

are either by specific cars or their

allogenic cars sitting 19 NK cars and.

You know, really also these comparative
randomized comparative studies introducing car T cells in the earlier lines of therapy. You know, we really took a set back with Chobit, but we really hope to be able to open all of these studies in the next few months and start enrolling patients. So this is. These are some of our instruct intra institutional research collaborations with Doctor Mina Xuan, Doctor Jordan Pober in Pathology, looking at the vasculature in the human lymphoma nodal micro environment human lymphoma nodal micro environment. Looking at these phase cars for low antigen expressing B cell cancers and
Then collaborations with City Chen.

So in the interest of time, I will just briefly discuss these collaborations, but.

As you know, getting the T cells to the tumor tissue and increasing homing is actually quite a challenge for most patients, and there have been several attempts to improve homing for lymphocytes.

Including cell surface painting, for example, to insert alphabeta integrin into primary lymphocytes, including glyco engineering CAR T cells,
for example, to enforce E selectin binding because as many of you may know, car T cells do not express sialyl Lewis X and do not bind deselctin, but we can actually achieve enforce their display on human CAR T cells by surface fucosylation and this will. Results in very robust E selectin binding even under conditions of hemodynamic shear and then also gene therapy using genetically modified lymphocytes targeting VEGF or two in highly vascularized tumors. But unfortunately all of this data is
in mice and we don’t really know what’s happening in the human tumor vessels, and we do not have any idea about the spatial relations of these two of these tumor infiltrating lymphocytes, and so the aim of our study is to employ highly multiplexed immunofluorescent imaging of human lymphomas to specially correlate and phenotype. The infiltrating even of sites using formalin fixed and not been embedded tissue specimens, and then we want to apply these results to investigate the informer vasculature in car T patients. Pretreatment and posttreatment.
This is Nathan Paulsen, one of the residents in pathology, and he’s already looked at some. Or lymphoma tissue samples showing that there are differences in expression levels of vascular adhesion molecules. For example, between diffuse large B cell lymphoma, classical Hodgkin lymphoma and T cell rich, large B cell lymphoma. And so we want to do high dimensional phenotyping of these vascular cell and in FPED identified tumor samples looking and all of these, all of these vascular markers and
the we anticipate to find some correlation of the vessel phenotypes with the abundance and phenotype of the leukocytic infiltrates and to correlate there this with the patients outcomes post car T cell therapy. If we’re lucky, we’re going to be able to show that some two rationale for combining antiangiogenic therapies, particularly. And this can be a launching point for us to actually eventually in the future consider a trial.
So this is some of the data from Chalet Sues Lab where he's using these face cars where.

Targeting specifically low density surface antigen and he's been able to show that car signaling is different from T cell receptor signaling and that it bypasses certain proteins like latch. And has a different pathway that results in acting polar MIS polymerization compared to TCR signaling, and he's. Actually using this information to develop these phase cars on lipid bilayers that he can modulate to recognize low density surface antigens.
So this is again some of the data that he is generated in his lab where he’s been able to show that Corti signaling bypasses this important scaffold. He’s been able to build this face where they contain and you control modality that can leverage domains affecting phase separation to modulate Carty activity recognizing low density surface antigens. He’s constructed Roger B cells expressing low to High City 19 and this is just some very preliminary data that he has showing that this point phase cars display superior...
01:04:23.961 --> 01:04:26.416 activity compared to control parties.

01:04:26.420 --> 01:04:26.881 Again, low against low CD 19 so we are hoping to look now at some of our patients blood samples that have.

01:04:30.569 --> 01:04:34.651 hoping to look now at some of our patients blood samples that have.

01:04:34.651 --> 01:04:37.289 patients blood samples that have.

01:04:37.290 --> 01:04:40.350 Low CD19 expressing he malignancy’s.

01:04:40.350 --> 01:04:43.410 either at baseline or following treatment with CD19 CAR T cell therapy.

01:04:43.509 --> 01:04:46.708 treatment with CD19 CAR T cell therapy.

01:04:46.708 --> 01:04:49.853 and and and showing how these pace cars will be able to to act against these low CD19 expressing tumors.

01:04:49.853 --> 01:04:53.384 cars will be able to to act against these low CD19 expressing tumors.

01:04:53.384 --> 01:04:55.894 these low CD19 expressing tumors.

01:04:55.900 --> 01:04:59.092 And then we’re also hoping the future to collaborate with City.

01:04:59.092 --> 01:05:01.811 future to collaborate with City.

01:05:01.811 --> 01:05:04.781 Chen looking at these dual knock.

01:05:04.781 --> 01:05:08.039 in knockout CAR T cells that he’s.
Engineered in his lab targeting two different antigens on lymphoma cells and and.

Doing PT one knockout.

So this is our.

This is our group and.

Dedicated really dedicated

group of people and I'm very thankful for their work and I went a little over time so I'm happy to answer any questions.

went a little over time so I'm happy to answer any questions.

So I don’t think there's any questions on the.

Chatroom at this point so.

I was thank you for a terrific presentation.

Thank you, thank you.